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Hepatolithiasis in Japan

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Introduction

The recent progress in imaging led to improvement of the diagnostic technology, and diversification of treatment methods. However, treatment of hepatolithiasis is difficult in many cases, because of its complicated clinico-pathological condition, and no method has been established yet for treatment of patients with intrahepatic stones.

We have recently conducted a nationwide survey of the incidence and clinico-pathological condition of hepatolithiasis, and compared its characteristics and chronological changes with those in other countries.

A large scale epidemiological investigation of hepatolithiasis in Japan was first carried out by the Research Group for the Study of Hepatolithiasis, Ministry of Health and Welfare of Japan¹⁾ in 1975. However, the investigations made so far covered only institutions having surgical departments. Therefore, the asymptomatic patients under observation only at the departments of internal medicine were overlooked, and consequently a clear picture of hepatolithiasis could not be grasped in terms of the number of patients. The present study, therefore, covered also those hospitals having only departments of internal medicine.

Subjects and Methods

Our study covered both departments of internal medicine and surgery at a total of 2,749 hospitals; 80 university hospitals, and other hospitals with more than 200 beds. First, a primary questionnaire was sent to these hospitals inquiring about the presence of any patients with hepatolithiasis. After checking their replies, investigation sheets for individual patients were sent, as a secondary questionnaire, asking in details about the age, symptoms, duration of illness, diagnostic methods for hepatolithiasis, past history of biliary tract diseases, types of hepatolithiasis, and so on.

The primary questionnaire was sent back from 1,437 institutions, and the rate of response was 52.3%. Of these respondents, 745 institutions had cases of hepatolithiasis during a 4-year period from 1989 to 1992. In total, we received investigation sheets for 1,887 patients with this disease.

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Key words: Hepatolithiasis, Epidemiology, National survey in Japan, Radiological diagnosis, Cholesterol stone

索引用語: 肝内結石, 疫学, 全国調査, 画像診断, コレステロール胆石

Results

1. Incidence of hepatolithiasis in Japan

There were 105,062 patients with cholelithiasis during the four year period from 1989 to 1992, and 2,353 patients of them (2.24%) had hepatolithiasis²⁾.

However, when the number is limited to those who underwent surgery, of the 73,480 patients who had operation for cholelithiasis, 1,280 (1.8%) had hepatolithiasis, showing a decrease in the incidence of hepatolithiasis (Fig. 1). In the first nationwide survey covering 1975–1985, the incidence of hepatolithiasis was 2.5%–3.0%¹⁾. In our present study, 1,813 of 79,052 (2.3%) patients with cholelithiasis at the surgical departments had hepatolithiasis, showing a further decreasing tendency compared to the previous nationwide statistics (1985–1988).

Regional analysis of the results of the present investigation revealed that the percentage of hepatolithiasis among patients with cholelithiasis was highest in Kyushu and Okinawa (south region, 3.6%), followed by Tohoku (north-eastern region, 3.4%), and lowest in Hokkaido area (Fig. 2).

2. Age of patients with hepatolithiasis

The ratio of male to female patients with hepatolithiasis was 1 : 1.3 (796 : 1,035). This ratio was 1 : 1.2 in an investigation of 954 patients covering 1973–1977¹⁾, and 1 : 1.2 in the previous nationwide survey, i.e., the ratio did not change during the past 20 years (Fig. 3).

In the present nationwide survey, the average ages were 59.1 years old in males and 59.3 years old in females, with no difference between both sexes. A comparison was made with 1973–1977 statistics regarding the age distribution of patients with hepatolithiasis, and the results revealed that the age of receiving the first treatment for hepatolithiasis is now about 10 years higher in all age groups due to the prolonged average life span (Fig. 4).

3. Past history of biliary tract disease in patients with hepatolithiasis

Of 1,871 patients with hepatolithiasis, as many as 788 (42.1%) had a past history of biliary tract surgery, and 72.3% of them had operation only once, while 22.2% had two operations. In case of

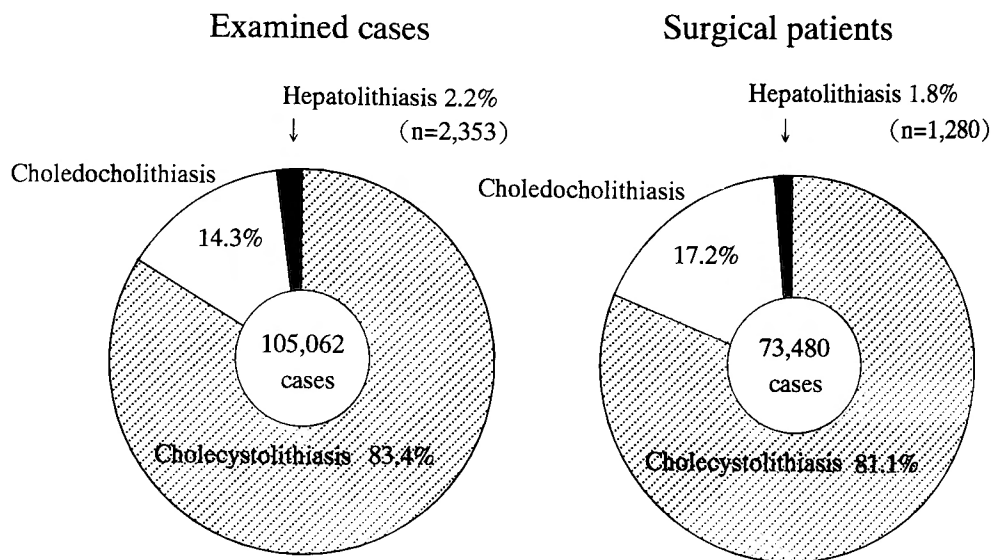


Fig. 1 Patients with Cholelithiasis in Japan (1989–1992)

the highest frequency, biliary tract surgery was performed as many as 6 times. This indicates the difficulty in treating hepatolithiasis (Table 1).

Analyzing the past history of biliary tract surgery in patients with hepatolithiasis revealed that cholecystolithiasis had the highest incidence.

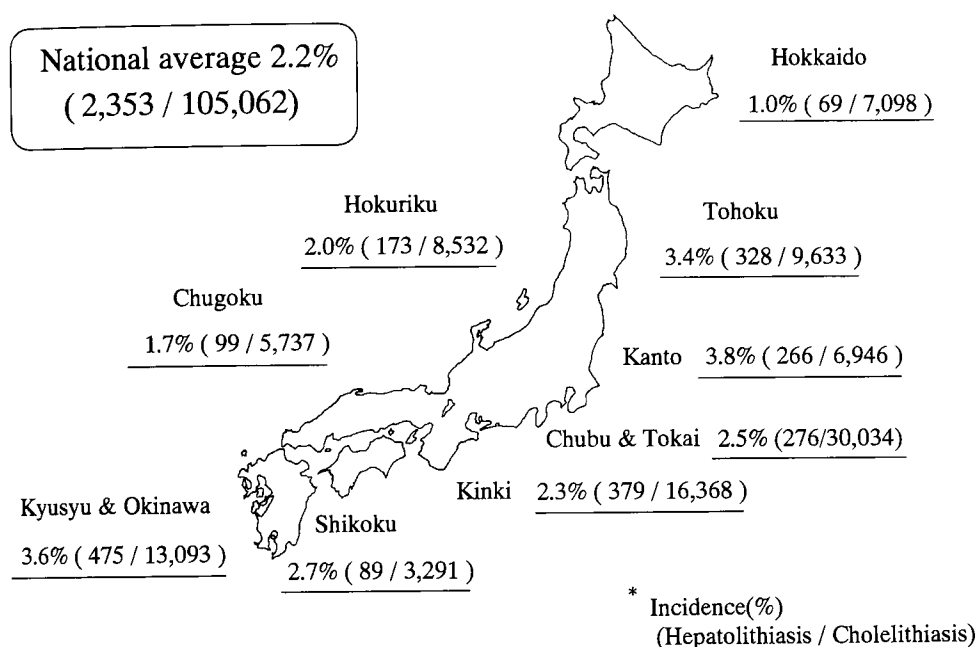


Fig. 2 Regional distribution of Hepatolithiasis among Cholelithiasis in Japan (364 Institutions) (1989-1992)

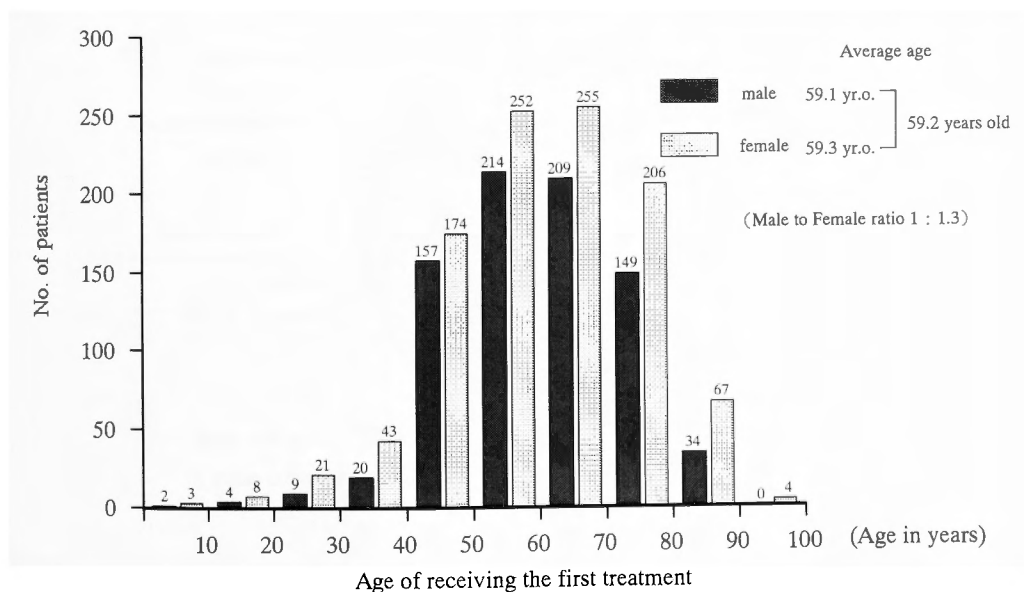


Fig. 3 Age of Patients with Hepatolithiasis

Of 788 patients who received treatment for hepatolithiasis, intrahepatic stones formed again in 182 patients (23.1%). Although many methods for stone treatment are now said to have reached a

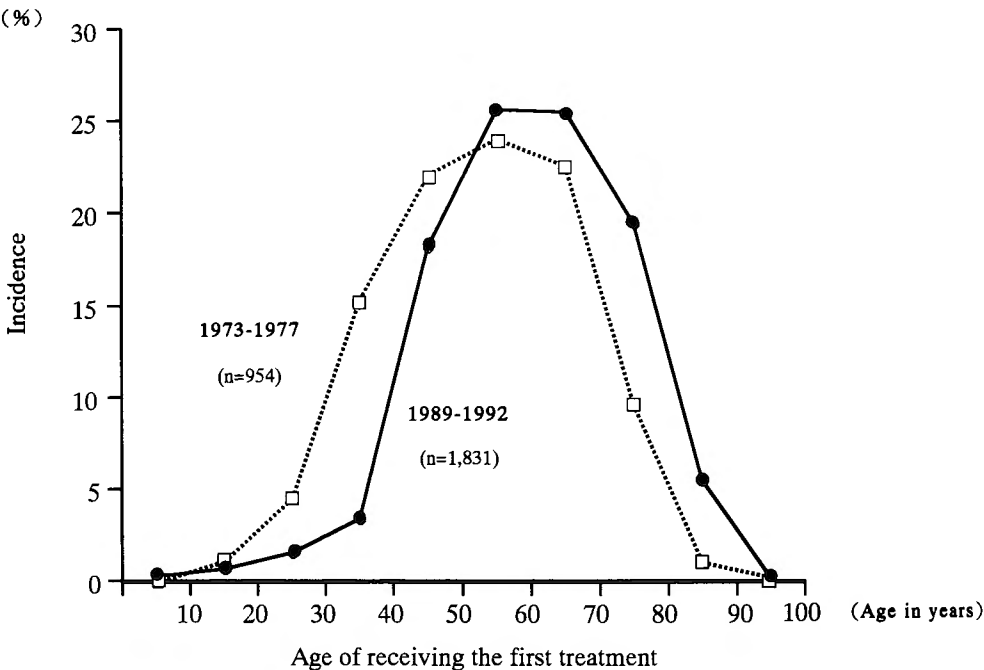
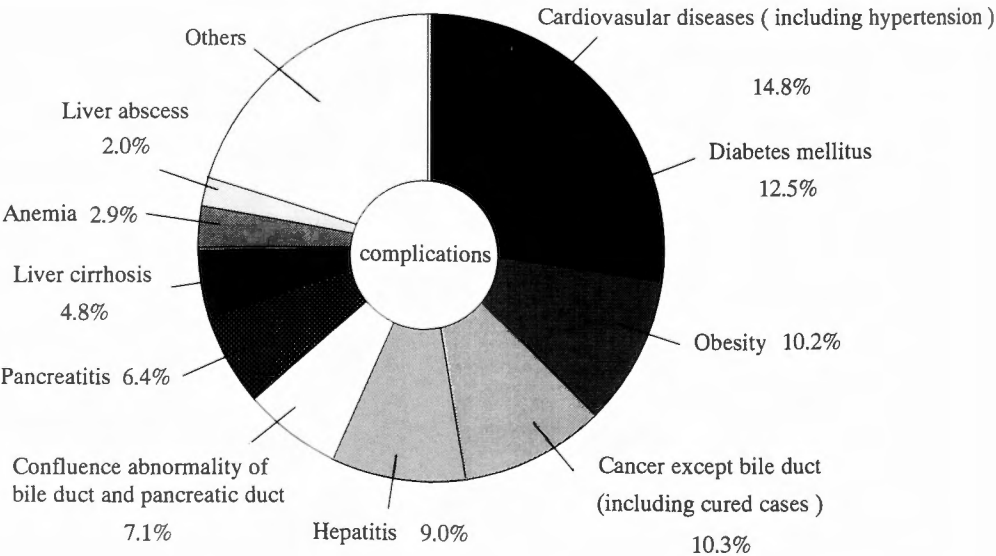


Fig. 4 Age of receiving the first Treatment for Hepatolithiasis



Patients with some complications / All patients : 901 / 1,753 cases (51.4%)

Fig. 5 Complications in patients with Hepatolithiasis

mature stage, the recurrence rate of hepatolithiasis is still very high (Table 2).

4. Present situation of the incidence of hepatolithiasis

The average during since the onset of symptoms of hepatolithiasis was 669 days. This is due to the fact that 117 patients suffering for more than 10 years were included in the patients investigated. The median value was 52 days, indicating that the patients already received treatment in a very early stage, i.e., within 1 to 3 months after the onset of symptoms (Table 3). This is attributed to the progress in diagnostic imaging that made it possible to diagnose the disease definitely as hepatolithiasis in a much earlier stage.

Here, it is very interesting to note that there were 296 patients (16.1%) who had no symptoms at all. Of patients with symptomatic hepatolithiasis, pain was observed in 1,220 (66.4%), and fever in

Table 1 Hepatolithiasis with Past History of Biliary tract Surgery
788/1,871 patients (42.1%)

frequency of operation	No. of patients	Rate (%)
Once	570	72.3
Twice	175	22.2
3 times	27	3.4
4 times	12	1.5
5 times	3	0.4
6 times	1	0.1

Table 2 Hepatolithiasis with past History of Biliary tract Diseases

Past history	No. of patients
Cholecystolithiasis	467
Choledocholithiasis (including cholecystolithiasis)	348
Hepatolithiasis (including cholecysto- and/or choledocholithiasis)	182
Others	134

Table 3 Duration from Onset of Symptoms due to Hepatolithiasis (n=1,795)

Duration of illness	No. of patients
No symptoms	288 cases
< 1 mo	304 cases
1 ≤ 3 mo	457 cases
3 ≤ 6 mo	171 cases
6 mo ≤ 1 yr	112 cases
1 ≤ 2 yr	112 cases
2 ≤ 5 yr	166 cases
5 ≤ 10 yr	68 cases
> 10 yr	117 cases

577 (31.4%). Gastrointestinal symptoms consisted mainly of nausea, vomiting and anorexia. Indefinite complaints included general malaise and edema (Table 4).

Meanwhile, 51.4% of patients with hepatolithiasis had other complications. Heart disease (14.8%) topped the list of complications, followed by diabetes mellitus (12.5%) and obesity (10.2%). This suggests that the patients with hepatolithiasis in Japan are also following the alimentary trends in Europe and U.S.A. (Fig. 5).

5. Changes in diagnostic methods for hepatolithiasis

Figure 6 shows the chronological changes—1975¹⁾, 1980¹⁾, 1985~1988²⁾, and 1989~1992—in reaching definite diagnosis of hepatolithiasis by various of diagnostic methods such as abdominal ultrasonography (US), computed tomography (CT), drip infusion cholangiography (DIC), endoscopic retrograde cholangiography (ERC), and percutaneous transhepatic cholangiography (PTC).

Table 4 Symptoms of Hepatolithiasis (n=1,838)

Symptoms	No. of patients
No symptoms	296
Abdominal pain	1,220
Fever	577
Jaundice	158
Gastrointestinal discomfort	31
Indefinite complaints	88

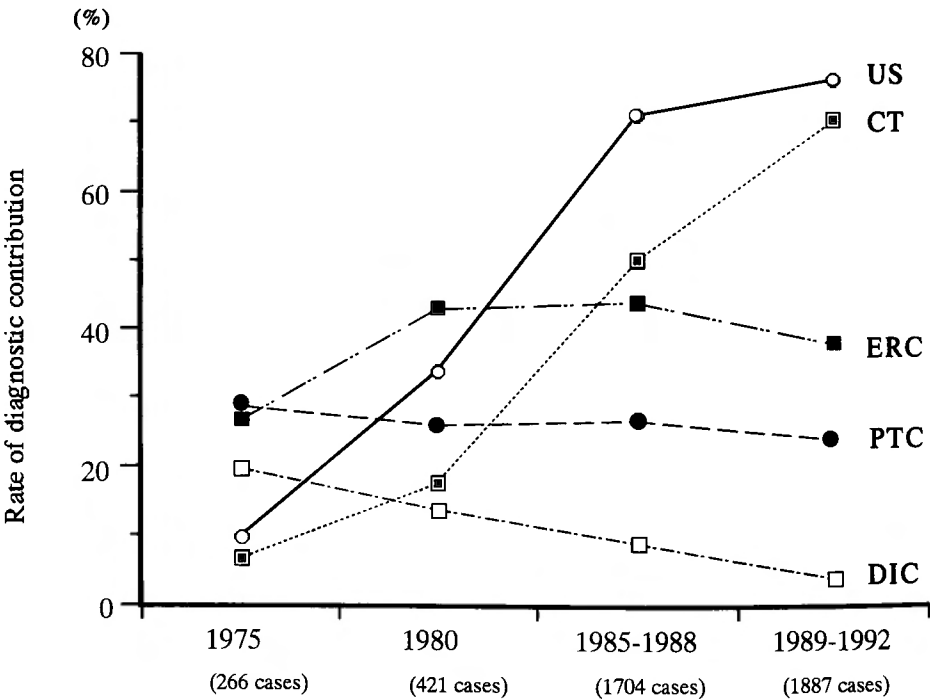


Fig. 6 Changes with Time in Diagnostic Method for Hepatolithiasis

About 20 years ago, US and CT were not widely used in Japan and their resolution power was very poor. Therefore, diagnosis depended mainly on direct imaging methods such as PTC and ERC. Also, 20% of the institutions still use DIC for definite diagnosis.

In 1980, however, US became prevalent in Japan, and its contribution to diagnosis rose to 34%, the second rank after ERC. In 1985, CT become widely used all over the country, and it became so popular that the rate of usage frequency in the diagnosis of hepatolithiasis reached 50% for the first time. In addition, as a result of improved US resolution, its diagnostic accuracy increased to 71%.

In 1990, the rate of diagnostic accuracy of US and CT exceeded 70%, and the combined use of both modalities facilitated detection of stones in 95% or more of the hepatolithiasis cases. On the other hand, the number of patients in whom intrahepatic stones were found during operation was 64 of 1,887 patients, i.e., only 3.4%.

6. Changes in classification of hepatolithiasis

The types of intrahepatic stones in 7,796 surgical patients were classified according to the Japanese hepatolithiasis classification. Firstly, regarding the IE classification, in 1975–1979, the rate of I type, a type limited to the intrahepatic bile ducts, was only 20.6%. However, the third nationwide survey in 1989–1992 showed a sharp increase up to 45.5%.

On the other hand, the rate of IE type, an intra and extrahepatic type which generally results from piling up of stones from the common bile duct, decreased to about 50% (Fig. 7). This is attributed to the feasibility and safety of choledocholithiasis surgery, and the possibility of removing stones in the extrahepatic bile duct at an early stage because of the widespread use of endoscopic therapy such as endoscopic duodenal sphincterotomy (EST).

Next, regarding the stones location in the liver, the left and right (LR) classification was employed. The rate of L type was about 45.5%, and did not change. Presumably, this is due to cholestasis which is liable to occur in the left lobe of the liver because of the structure of the bile duct. Concerning LR type which affects both lobes of the liver, the total of LR, LR and LR was only 26.3%, and the figure almost persisted in the second nationwide survey in 1985–1988 (Fig. 8).

Fig. 9 shows the age distribution of IE type in patients with hepatolithiasis in the present

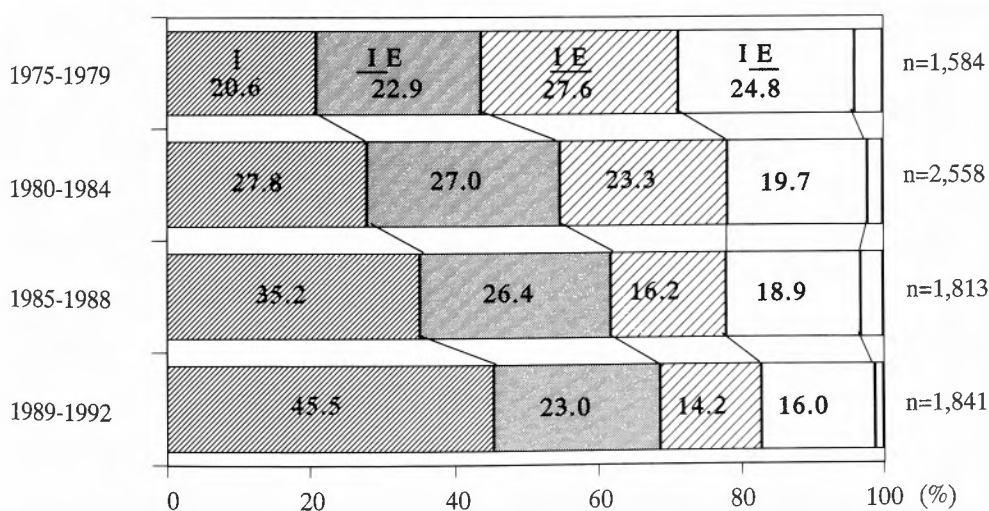


Fig. 7 Hepatolithiasis Type (I and IE typing)

survey. The rate of I type in patients under 24 years old was 76.7%, and it decreased gradually with aging, reaching 33.7% in those aged 75 or over. This indicates that many young patients have primary hepatolithiasis, while elder patients have secondary intrahepatic stones and choledocholithiasis (Fig. 9).

7. Components of intrahepatic stones

In the past, intrahepatic stones were reported to consist mainly calcium bilirubinate by macroscopic inspection only and no further analysis was performed. Recently, however, increasing cases of cholesterol stones have been reported even among the intrahepatic stones.

In the present nationwide survey, stones were analyzed in 1,375 patients, and 74.8% of them had calcium bilirubinate stones, while 13.1% (180 patients) had cholesterol stones. Of these patients with cholesterol stones, 31 (17.2%) had intrahepatic pure cholesterol stones. In addition, 51.1% had mixed stones, and 13.3% had combination stones (Table 5).

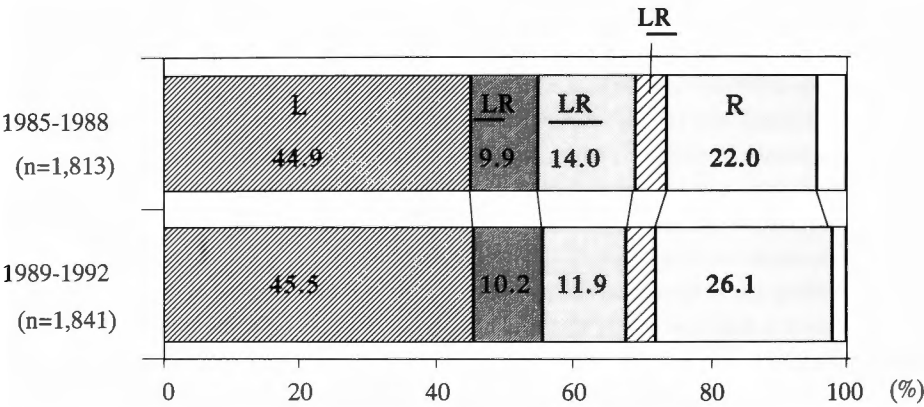


Fig. 8 Hepatolithiasis Type (existing side of stones L R)

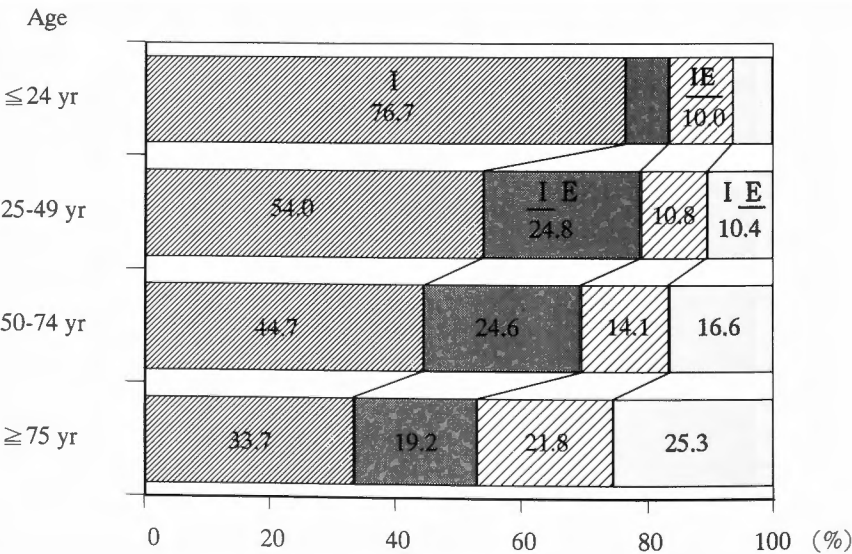


Fig. 9 Age Distribution in IE Type Hepatolithiasis

Stones were analyzed by the infra-red rays in 286 patients with hepatolithiasis, and the results were as follows. The calcium bilirubinate content was the highest (43.8%), followed by cholesterol (39.0%), which was higher than expected, and then was fatty acid-calcium (14.4%). These three major components constituted about 96% of these stones (Table 6).

Discussion

On making comparisons between various countries, it is necessary to consider involvement of the environmental factors, such as the hygienic environment and daily diet in each country. In Europe and U.S.A., the percentage of hepatolithiasis/cholelithiasis is very small (1–2%), and therefore hepatolithiasis is regarded as a very rare disease. Table 7 shows the incidence of hepatolithiasis in some foreign countries^{1–16}. Even in Europe and U.S.A., the incidence of hepatolithiasis was 5–10% before 1960. However, it decreased rapidly in the past 20 years. On the other hand, in the East-Asian countries such as Japan, Korea, China, and Taiwan, it is still 10–40%¹⁵. Table 4 shows the incidence of hepatolithiasis in Korea, Taiwan, and China, which is higher than that in Japan^{14–16}.

We cannot judge whether the incidence of hepatolithiasis in Japan in particular is higher or not than that in the so-called white men since the clinico-pathological condition and pathogenesis of hepatolithiasis have not been fully clarified. Besides, the diagnostic capability differs in each country. In Japan, the studies on segmental dissection of the intrahepatic bile ducts, and on defining the

Table 5 Complication of Intrahepatic Stones

Classification of stones	No. of patients
Calcium bilirubinate stone	1,028 (74.8%)
Cholesterol stone	180 (13.1%)
Pure cholesterol stone	31
Mixed stone	92
Combined stone	29
Others	28
Black stone	120 (8.7%)
Calcium fatty acid stone	39 (2.8%)
Others	8
Total	1,375 cases

Table 6 Clinical Analysis of Components of Intrahepatic Stones (n=286)

Component	Vol %
Cholesterol	39.0±36.6
Calcium bilirubinate	43.8±32.1
Calcium fatty acid	14.4±19.2
Calcium carbonate	0.9±7.1
Calcium phosphate	0.8±8.3
Protein	0.6±7.0
Unknown	0.5±1.1

mode of their confluence by diagnostic imaging are said to have reached a mature stage. However, the present situation is that the results of these studies have not been fully applied to the treatment.

In Japan, the percentage of hepatolithiasis/cholelithiasis was 10–15% in the 1940's and 1950's, but it sharply decreased to 3.0% in 1975¹⁷⁾, and further to 2.2% in the present survey. It should be noted, however, that the incidence in Japan showed regional variations ranging from 1.0% in Hokkaido to 3.6% in Kyushu and Okinawa. In particular, it was 27–30% in Nagasaki in Kyushu¹⁸⁾ which is 10 times or more higher than in other regions. Hitherto, it has generally been reported that the incidence of hepatolithiasis is higher in the rural or agricultural areas than in the urban areas. Epidemiologically, this is ascribed to life style, daily dietary habits, and nutritional status.

It is true that in the past, the Japanese people in the rural or agricultural areas ate less vegetables compared to urban people, and their foods consisted mainly of potatoes, grain, fish and shellfish. However, with the progress in transportation networks and commodity distribution system, the remarkable differences in life style between the two areas disappeared. Also, the quality test of tap water showed no major differences between the two areas in pH, hardness, bacteria, and organic substances. In addition, as the familial incidence is high, a recent report suggested involvement of genes, such as HLA antigen, in the pathogenesis of hepatolithiasis¹⁴⁾.

With the decrease in the incidence of hepatolithiasis, a change has also been observed in the disease type. In 1975, IE type (intra- and extra hepatic stones) was the major type. In the present investigation, however, I type (intrahepatic stones only) constituted about 50% of the patients. However, there are still a considerable number of patients with “piled-up type” (IE type) in East-Asian countries, such as China, Korea, and Taiwan, where the incidence of hepatolithiasis is higher than in Japan. This “piled-up type” eventually leads to an increase in LR type (Table 8). This is clearly manifest in the present trend in Japan where the percentage of I type is as high as 76.7% in young pa-

Table 7 Incidence of Hepatolithiasis in foreign Countries

Reported by	(Year)	Country	Total No. of cholelithiasis	No. of hepatolithiasis	Incidence (%)
Best ¹⁾	(1944)	USA	456	35	7.6
Chin-Chiiang ²⁾	(1959)	China	NM	110	30.0
Glenn ³⁾	(1961)	USA	169	22	13.0
Bove ⁴⁾	(1963)	Brazil	2,000	20	1.0
Shore ⁵⁾	(1970)	USA	123	30	2.4
King ⁶⁾	(1971)	Malaysia	661	120	18.1
Balasegaram ⁷⁾	(1972)	Malaysia	NM	68	10.2
Lindstrom ⁸⁾	(1977)	Sweden	804	5	0.6
Simi ⁹⁾	(1979)	Italy	2,700	36	1.3
Chen ¹⁰⁾	(1984)	China	362	162	44.8
Nakayama ¹¹⁾	(1984)	Singapore	647	11	1.7
		Hong Kong	700	22	3.1
Yamuch ¹²⁾	(1989)	Chile	17,200	251	1.5
Gandini ¹³⁾	(1990)	Italy	NM	73	1.0
Nakayama ¹⁴⁾	(1991)	China (Shenyang)	394	83	21.1
		China (Beijing)	422	39	9.2
Su ¹⁵⁾	(1992)	Taiwan	17,182	3,486	20.3
Han ¹⁶⁾	(1992)	Korea	1,344	145	10.8

Table 8 Incidence of Hepatolithiasis in East Asia

		Total cholelithiasis	No. of hepatolithiasis (%)	Male to female ratio	I : IE	L : LR : R
China ¹⁴⁾ (1978-1983)	Shenyang	394	83 (21.1)	1 : 1.2	25 : 75	17 : 73 : 10
	Beijing	422	39 (9.2)		5 : 95	
Korea ¹⁶⁾ (1986-1990)	Seoul	1,344	145 (10.8)	1 : 1.4	26 : 74	30 : 54 : 16
Taiwan ¹⁵⁾ (1971-1989) at 28 Institutions		17,182	3,486 (20.3)	1 : 1.3		40 : 39 : 17 39 : 24 : 37

tients under 24 years of age, and the percentage of IE type increases with aging.

Generally, stones seldom move in I type, and therefore the patients are commonly asymptomatic, and the stones are detected accidentally by CT or US in many cases. In fact, hepatolithiasis was diagnosed in 16.1% of the patients although they had no symptoms (Table 3). This suggests that a phenomenal progress has been attained in diagnostic imaging during the past several years. Until 20 years ago, the main definite diagnostic methods were direct imaging methods such as ERC and PTC, and 20% of the institutions depended on DIC (Fig. 6). However, from the latter half of 1980's, US and CT became widely used. Especially, it has recently become possible, with the aid of US patterns and CT values, not only to specify the location of intrahepatic stones, but also to infer even the chemical components of the stones, thereby providing helpful information for formulation of treatment policy.

Meanwhile, great changes have been recently observed in the components of these stone. In the past, intrahepatic stones were considered to consist mainly of calcium bilirubinate¹¹⁾. In fact, macroscopic classification showed that 74.8% of the intrahepatic stones consisted of calcium bilirubinate. However, the analysis of stone components made in 286 patients by infra-red rays revealed that calcium bilirubinate constituted 43.8%, and cholesterol 40% on the average. We may say that as a result of westernization of living and life style of the Japanese, the cholesterol content tends to increase in the intrahepatic stones. It is expected that in the future, the incidence of hepatolithiasis will decrease to about 1% as in Europe and U.S.A., with a resultant increase in cholesterol stones.

Regarding the mechanism of formation of intrahepatic cholesterol stones and the epidemiological background in particular, it is necessary to study how it should be diagnosed and treated. However, since there are few reports in other countries on intrahepatic cholesterol stones, this will be an important subject of study hereafter in Japan.

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和文抄録

日本における肝内結石症の現状

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肝内結石症はその病態の複雑さのために治療が困難なことが多く、確立した治療法がまだ定まっていないのが現状である。今回、肝内結石症の発生状況とその病態について1989年から1992年に経験した肝内結石症について全国アンケート調査を行い、その変遷と特徴について他国と比較検討した。対象としたのは200床以上の病院および大学病院の内科・外科の計2,749施設で、アンケート回答の施設数は1,437施設と回収率は52.3%であった。そのうち、1989～1992年の4年間に肝内結石症を経験した施設は745あり、1,887例の肝内結石症例の個人調査表を送付いただいた。

1989～1992年における肝内結石症の頻度は、総胆石症例105,062例のうち肝内結石症は2,353例（2.24%）であった。しかし手術施行症例に限定すると、胆石症としての手術73,480例のうち、肝内結石症は1,280例（1.8%）に留まった。地域別の検討では、肝内結石症の胆石症に占める頻度が最も高いのは九州・沖縄地方で3.6%、次いで東北地方の3.4%と続き、北海道地方は最も少なかった。

肝内結石症1,871例のうち、胆道手術の既往を有する症例は42.1%にあたる788例もあり、肝内結石症の治療後にまた肝内結石を再発した症例も788例中182例、23.1%と極めて多く、治療の困難性が示された。

肝内結石症の確定診断に有用であった検査を検索すると、US と CT の肝内結石症における診断能は70%を越え、両診断法を併せると95%以上の肝内結石症では存在診断が可能となり、逆に、術中にはじめて肝内結石の存在が判明した症例は1,887例のうち64例とわずか3.4%に過ぎない。

肝内結石症の病型分類の変遷を IE 型で示すと、1975～1979年には肝内胆管に限局する I 型はわずか20.6%に過ぎなかったのが、今回の全国調査では45.5%に激増し、逆に、一般に総胆管結石が積み上げられたとされる IE 型は IE 型はほぼ半減した。

肝内結石の種類について従来は、肝内結石といえばビリルビンカルシウム石であるとされていたが、今回の全国調査では、結石の種類について記載のあった1,375例中、ビリルビンカルシウム石は74.8%で、コレステロール胆石も13.1%にあたる180例に認められていた。しかも純コレステロール石の肝内結石が31例で17.2%もあり、そのほか混合石51.1%、混成石13.3%であった。